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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,109	06/22/2006	Kenichiro Kosai	55801-003US1	8348

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/584,109	KOSAI ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application was transferred to examiner Quang Nguyen, Ph.D. in AU 1633.

Applicant's amendment filed on 10/29/2008 was entered.

Amended claims 1-27 and new claim 28 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claim 14 is objected to because the term "tachyacardia" is misspelled. Appropriate correction is required.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 14-25 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection.***

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the

filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method for treating a heart disease comprising expressing a CD9 gene in the heart of a subject in need thereof, wherein the heart disease is characterized by myocardial infarction, hypertrophy, arrhythmia or tachycardia. The instant claims encompass the use of any expression inducing substance for expressing endogenous CD9 gene (see at least dependent claim 27) as well a gene therapy agent used for transferring a CD9 gene other than an expression vector comprising a CD9 gene (see at least dependent claims 25-26)

Apart from the disclosure of using an expression vector encoding a CD9 protein , **the specification fails to describe the essential characteristics or elements possessed by a single expression inducing substance for expressing endogenous CD9 gene, let alone for a representative number of species for a broad genus of "an expression inducing substance for expressing endogenous CD9", or any other gene therapy agent for transferring a CD9 gene to be used in the method as broadly claimed**. For example, what are the relevant structures possessed by an expression inducing substance for expressing endogenous CD9 gene or other gene therapy agent used for transferring a CD9 gene to be used in the methods as claimed?

At about the effective fling date of the present application (12/24/04), little was known about expressing inducing substance for expressing endogenous CD9 gene or gene therapy agents other than an expression vector for transferring a CD9 gene to be utilized in a treatment method as broadly claimed as evidenced at least by the teachings of Iwamoto et al (Cytokines & Growth factor reviews 11:335-344, 2000; IDS), Berditchevski, F (J. Cell Science 114:4143-4151, 2001; IDS) and Verma et al. (Annu. Revi. Biochem. 74:711-738, 2005).

Thus, the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a representative number of species for a broad genus of **"an expression inducing substance for expressing endogenous CD9", or any other gene therapy agent apart from an expression vector for transferring a CD9 gene to be used in the method as broadly claimed**, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25

USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112 - Enablement

Amended claims 14-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for suppressing cardiac hypertrophy or cardiac tachycardia in a subject having a heart disease, said method comprises administering directly to a cardiac muscle in the heart of said subject an expression vector comprising a sequence encoding a CD9 protein, wherein the heart disease is characterized by myocardial infarction, hypertrophy, arrhythmia or tachycardia, and wherein cardiac hypertrophy or cardiac tachycardia is suppressed in said subject;

does not reasonably provide enablement for <u>any other method for treating a heart disease characterized by myocardial infarction, hypertrophy, arrhythmia or tachycardia by simply expressing a CD9 gene in the heart of any subject in need as broadly claimed</u>. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention commensurate in scope with these claims. ***This is a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)). ***This is a new ground of rejection.***

The instant specification is not enabled for a method for treating a heart disease comprising expressing a CD9 gene in the heart of a subject in need thereof, wherein the heart disease is characterized by myocardial infarction, hypertrophy, arrhythmia or tachycardia as broadly claimed for the following reasons.

1. The breadth of the claims

The claims are directed to a method for treating a heart disease comprising expressing a CD9 gene in the heart of any subject in need thereof, not necessarily limited to a subject already has symptoms of a heart disease (see at least dependent claims 25 and 27), by any means and not necessarily limited to the administration of an expression vector encoding CD9 and/or via any route and/or site in the treated subject (see at least dependent claims 25-28) to attain any desired treatment outcomes (e.g., prophylactic and/or therapeutic effects), and wherein the heart disease is characterized by myocardial infarction, hypertrophy, arrhythmia or tachycardia.

2. The state of the prior art and the unpredictability of the prior art

At the effective filing date of the present application (12/24/04), virtually nothing was known that CD9/DRAP27 could possess therapeutic activity in a heart disease as evidenced at least by the reviews of Iwamoto et al (Cytokines & Growth factor reviews 11:335-344, 2000; IDS) and Berditchevski, F (J. Cell Science 114:4143-4151, 2001; IDS). CD9/DRAP27 protein is known to be closely associated with proHB-EGF in the cell membrane, and that co-expression of CD9/DRAP27 with proHB-EGF markedly enhances diphtheria toxin (DT) binding and DT sensitivity of cells (Higashiyama et al., J. Cell Biol. 128:929-938, 1995; IDS). Nishida et al. (Arterioscler. Thromb. Vasc. Biol. 20:1236-1243, 2000; IDS) also disclose that CD9 is involved in the process of artherogenesis by promoting the proliferation of smooth muscle cells as an enhancer of proHB-EGF via the juxtacrine growth pathway and that CD9 is localized immunohistochemically in the SMCs of the artherosclerotic aorta and coronary arteries. Moreover, enhanced expression of HB-EGF has been observed under pathological conditions such as cardiac hypertrophy and myocardial infarction (Fujino et al., Cardiovascular Research 38:365-374, 1998; Tanaka et al. Biochem. Biophys. Res. Commun. 297:375-381, 2002).

Furthermore, the nature of the instant claims falls within the realm of gene therapy. At the effective filing date of the present application (12/24/04), the attainment of any therapeutic effect via gene therapy was and remains highly unpredictable. **There are several known factors that limit an effective human gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most**

importantly an efficient gene delivery to target tissues or cells. Romano et al. (Stem Cells 18:19-39, 2000) state "The potential therapeutic applications of gene transfer technology are enormous. However, **the effectiveness of gene therapy programs is still questioned**", and "[d]espite the latest significant achievements reported in vector design, **it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame**" (see abstract, col. 2). Even in 2005, Verma et al. (Annu. Revi. Biochem. 74:711-738, 2005) still state "The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to heart disease and cancer. It has, therefore, generated great hopes and great hypes, but **it has yet to deliver its promised potential**", and "[I]f scientists from many different disciplines participate and pull together as a team to tackle the obstacles, **gene therapy will be added to our medicinal armada** and the ever-expanding arsenal of new therapeutic modalities." (page 732, top of third paragraph). Goncalves (BioEssays 27:506-517, 2005) also states "Overall, one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (page 514, right-hand column, last paragraph). Gardlik et al. (Med. Sci. Monit. 11:RA110-121, 2005) conclude "Although clinical trials have already started, **there are still numerous limitations that must be solved before routine clinical use**.

Nevertheless, it can be expected that **future research will bring tissue- and disease-specific delivery strategies and that this hurdle will be overcome at last**" (page RA119, right-hand column, last paragraph).

3. The amount of direction or guidance provided

Apart from the exemplifications showing that over-expression of exogenous CD9 mediated by adenoviral transduction in cardiac cells in both *in vitro* and *in vivo* resulted in the suppression of both cardiac cell volume and cardiac beating rates for cardiac cells stimulated by angiotensin II and recombinant HB-EGF, and cardiac cells in a mouse ischemic heart failure model, the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain any other therapeutic effects (e.g., regeneration and/or repair the diseased heart to a healthy original state) and/or any prophylactic effect (e.g., preventing the onset of the recited heart disease for any period of time such as 1 week, 1 month, 1 years to several years in a subject in need thereof) within a broad "treatment" scope for any subject in need thereof, including a subject that does not have any symptom of a heart disease, in the method as claimed. Additionally, the instant specification also fails to teach a single agent or substance that is used to induce the expression of endogenous CD9 protein in the heart of a treated subject at an effective level to attain the desired prophylactic and/or therapeutic effects. Moreover, the instant specification also fails to provide any guidance for a skilled artisan on how to overcome obstacles associated with in vivo vector targeting known in the gene therapy art, so that an expression vector encoding CD9 protein can be delivered at any site and/or by any route of delivery (e.g, oral, mucosal, intravenous deliveries) in the treated subject and

the expression vector can still reach targeted cardiac muscle cells in an effective amount to yield the desired prophylactic and/or therapeutic effects. Since the prior art at the effective filing date of the present application does not provide such guidance for the above mentioned issues, it is incumbent upon the present application to do so. Therefore, at least in light of the state of the gene therapy art and the state of the art on treating a heart disease with CD9/DRAP27, coupled with the lack of sufficient guidance provided by the instant specification it would have required undue experimentation for a skilled artisan to make and use the treatment method as broadly claimed.

Furthermore, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the state of the relevant physiological and gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Applicant's arguments in the Amendment filed on 10/29/08 (pages 7-10) with respect to the previous Enablement rejection in the Office action mailed on 6/30/08

have been considered. However, it is noted that Applicant's arguments were not directed to new grounds of rejection as set forth in the above new enablement rejection with a new scope of enablement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-11 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Claims 2-3, 5-6, 10 and their dependent claims recite the limitation "the heart disease" in line 2 of the claims. There is insufficient antecedent basis for this limitation in the claim. This is because in claim 1 from which these claims are dependent on there is no recitation of any heart disease.

In claim 23, it is unclear what is encompassed by the phrase "arrhythmia-inducing right ventricular dysplasia (ARVD, ARVC)". What does the term "ARVC" stand for? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Amended claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyake et al (Oncogene 19:5221-5226, 2000). ***This is a new ground of rejection necessitated by Applicant's amendment.***

The claims are directed to a drug comprising an expression vector containing a CD9 gene as the active ingredient and a pharmaceutically acceptable auxiliary or carrier. It is further noted that for a composition claim, its intended use is not given any patentable weight in light of the prior art.

Miyake et al already disclose a composition comprising a replication-deficient adenovirus encoding MRP-1/CD9 cDNA in virus dialysis buffer (a pharmaceutically acceptable auxiliary or carrier) for intratumoral injection; and the composition results in a 73.7% reduction in the number of pulmonary metastasis of mice and a significantly longer median survival time of mice treated with rAd-MRP-1/CD9 relative to mice treated with the rAd-β-gal vector (see at least the abstract; page 5225, col. 1, top of second paragraph and col. 2, section titled "MRP-1/CD9 gene therapy").

The composition of Miyake et al is indistinguishable from the drug as claimed. Accordingly, the reference anticipates the instant claims.

Claims 1-18, 23-26 and 28 are rejected under 35 U.S.C. 102(a) as being anticipated by Ushikoshi et al (Circulation, Supplement III, 110, page 8, 2004). ***This is a new ground of rejection.***

Ushikoshi et al already disclosed a method of injecting directly into the heart of a mouse with an ischemic heart failure (generated by making myocardial infarction) a recombinant adenoviral vector encoding CD9, and they found that CD9 gene therapy reduced mortality, decreased heart weight and improved cardiac function in the treated mouse compared with mice in control groups.

Accordingly, the teachings of Ushikoshi et al meet the limitation of the instant claims. Therefore, the reference anticipates the instant claims.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633